

Amendments to the Specification

Please amend paragraph [0114] appearing on page 54 of the specification as follows:

It has been reported that tyrosine kinase inhibitors, such as STI571 (Imatinib mesilate, Gleevee GLEEVEC[®]), have potent synergetic effect in combination with other anti-leukemic agents, such as etoposide (Liu, W.M., *et al. Br. J. Cancer* 86:1472-1478 (2002)). Therefore, another embodiment of the present invention is directed to compositions and methods effective to inhibit neoplasia comprising an AIP binding compound, or a pharmaceutically acceptable salt or prodrug of an AIP binding compound described herein, which functions as a caspase cascade activator and inducer of apoptosis, in combination with at least one known tyrosine kinase inhibitor, or a pharmaceutically acceptable salt of the agent. Examples of known tyrosine kinase inhibitors, which can be used for combination therapy include, but are not limited to, gleevee GLEEVEC[®], ZD1839 (Iressa IRESSA[®]), SH268, genistein, CEP2563, SU6668, SU11248, and EMD121974.

Please amend paragraph [0118], appearing on page 56 of the specification as follows:

It has been reported in clinical studies that regular administration of non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk of breast cancer. ~~See Study: Why aspirin, fiber prevent cancer, posted Wednesday, April 9, 2003 at <http://www.cnn.com/2003/Health/04/09/health.cancer.aspirin.reut/index.html>.~~ It has also been reported that in colon cancer cells, NSAIDs prevent interleukin-6 from activating STAT1; STAT1 prevents cellular suicide. ~~Id.~~ Hence, NSAIDs are believed to make cells more conducive to apoptosis. Therefore, another embodiment of the present invention is directed to compositions and methods effective to inhibit neoplasia comprising an AIP binding compound, or a pharmaceutically acceptable salt or prodrug of an AIP binding compound described herein, which functions as a caspase cascade

activator and inducer of apoptosis, in combination with at least one known NSAID, or a pharmaceutically acceptable salt of the agent. Examples of known NSAIDs, which can be used for combination therapy include, but are not limited to, ibuprofen, aspirin and sulindac.

Please amend paragraph [0308], appearing on page 156 of the specification as follows¹:

An NCBI Blast search (~~accessible at <http://www.ncbi.nlm.nih.gov/BLAST/>~~) using this peptide revealed that it is a part of SEQ ID NO: 1 or 4.

| <u>Sequence</u> | <u>aa Positions</u> |
|-----------------|--|
| VSASPLLYTLIEK | amino acids 496-508 of SEQ ID NO. : 1 or 4 |

EXAMPLE 34

Isolation and Identification of Transferrin Receptor

Isolation of transferrin receptor from plasma membrane fraction of Jurkat cells by gambogyl affinity chromatography:

Please amend paragraph [0315], appearing on pages 159-160 of the specification as follows:

The following lists the experimentally deduced peptide sequences having the closest fitting calculated molecular weights. An NCBI Blast search (~~accessible at <http://www.ncbi.nlm.nih.gov/BLAST/>~~) using these peptides revealed that they are a part of SEQ ID NO: 1 or 4.

¹ Underlining of "Sequence" and "aa Positions" is as it appears in the original.

| <u>Sequence:</u> | <u>aa positions</u> |
|------------------|--|
| AVLGTSNFK | amino acids 487-495 of SEQ ID NO.: 1 or 4 |
| GFVEPDHYVVVGAQR | amino acids 395-409 of SEQ ID NO.: 1 or 4 |
| ILNIFGVIK | amino acids 386-394 of SEQ ID NO.: 1 or 4 |
| LAVDEEENADNNTK | amino acids 40-53 of SEQ ID NO.: 1 or 4 |
| LLNENSYVPR | amino acids 146-155 of SEQ ID NO.: 1 or 4 |
| LTDFGNAEK | amino acids 656-665 of SEQ ID NO.: 1 or 4 |
| LVYLVENPGGYVAYSK | amino acids 209-224 of SEQ ID NO.: 1 or 4 |
| SAFSNLFGGEPLSYTR | amino acids 7-22 of SEQ ID NO.: 1 or 4 |
| SSGLPNIPVQTISR | amino acids 326-339 of SEQ ID NO.: 1 or 4 |
| VSASPLLYTLIEK | amino acids 496-508 of SEQ ID NO.: 1 or 4 |

EXAMPLE 35

Immunofluorescence, Immunohistochemistry, and Electron Microscopy

Please amend paragraph [0340], appearing on pages 170-171 of the specification as follows:

The following table lists the experimentally determined molecular weights, Mr(expt), of the column fractions, and peptides having the closest fitting calculated molecular weight, Mr(calc). The difference between Mr(expt) and Mr(calc) is indicated

as "Delta." An NCBI Blast search (~~accessible at <http://www.ncbi.nlm.nih.gov/BLAST/>~~) using these peptides revealed that they are a part of SEQ ID NO: 34. Query refers to the sample number, Observed is the m/z ratio, Mr(expt) is the experimental mass adjusted for charge, Mr(calc) is the predicted peptide mass, Delta is the difference between the experimental and calculated mass, and Peptide is the amino acid sequence.

Please amend paragraph [0345], appearing on pages 175-176 of the specification:

The following table lists the experimentally determined molecular weights, Mr(expt), of the column fractions, and peptides having the closest fitting calculated molecular weight, Mr(calc). The difference between Mr(expt) and Mr(calc) is indicated as "Delta." An NCBI Blast search (~~accessible at <http://www.ncbi.nlm.nih.gov/BLAST/>~~) using these peptides revealed that they are a part of SEQ ID NO: 36. Query refers to the sample number, Observed is the m/z ratio, Mr(expt) is the experimental mass adjusted for charge, Mr(calc) is the predicted peptide mass, Delta is the difference between the experimental and calculated mass, and Peptide is the amino acid sequence.

| Query | Observed | Mr(expt) | Mr(calc) | Delta | Peptide |
|-------|----------|----------|----------|-------|---|
| 225 | 465.51 | 929.00 | 930.50 | -1.50 | TALQEEIK (amino acids 1028-1035 of SEQ ID NO.: 36) |
| 254 | 508.23 | 1014.44 | 1014.49 | -0.05 | MLQHAASNK+Oxidation (M) (amino acids 1231-1239 of SEQ ID NO.: 36) |
| 287 | 547.15 | 1092.28 | 1092.48 | -0.19 | LTAEEMDER (amino acids 26-34 of SEQ ID NO.: 36) |
| 312 | 589.01 | 1176.00 | 1175.57 | 0.44 | EDSNLTLQEK (amino acids 1446-1455 of SEQ ID NO.: 36) |
| 331 | 617.58 | 1233.14 | 1232.59 | 0.55 | FPDAGEDELLK (amino acids 1175-1185 of SEQ ID NO.: 36) |
| 502 | 735.11 | 1468.20 | 1467.66 | 0.55 | VDFTEEEINNMK (amino acids 175-186 of SEQ ID NO.: 36) |
| 508 | 742.83 | 1483.64 | 1483.65 | -0.01 | VDFTEEEINNMK |

| | | | | | |
|-----|--------|---------|---------|-------|---|
| | | | | | +Oxidation (M) (amino acids 175-186 of SEQ ID NO.: 36) |
| 509 | 745.88 | 1489.74 | 1489.76 | -0.02 | SVKEDSNLTLQEK (amino acids 1443-1455 of SEQ ID NO.: 36) |
| 535 | 783.23 | 1564.44 | 1564.65 | -0.20 | FDVPGDENAEMDAR (amino acids 1369-1382 of SEQ ID NO.: 36) |
| 539 | 791.27 | 1580.52 | 1580.64 | -0.12 | FDVPGDENAEMDAR +Oxidation (M) (amino acids 1369-1382 of SEQ ID NO.: 36) |
| 561 | 544.15 | 1629.43 | 1628.72 | 0.71 | NKEQLSDMMMINK +3 Oxidation (M) (amino acids 941-953 of SEQ ID NO.: 36) |

EXAMPLE 43

Isolation and Identification of Heat Shock Protein

Isolation of heat shock protein from plasma membrane fraction of Jurkat cells by gambogyl affinity chromatography:

Please amend paragraph [0352], appearing on page 179 of the specification, as follows:

The following table lists the experimentally deduced peptide sequences having the closest fitting calculated molecular weights. An NCBI Blast search (~~accessible at~~ <http://www.ncbi.nlm.nih.gov/BLAST/>) using these peptides revealed that they are a part of SEQ ID NO: 38.

Sequence:

ADLINNLGTIAK
AKFENLCK
ALLFIPR
ELISNASDALDK
ELISNASDALDKIR
ELKIDIIPNPQER
EQVANSADFVER
FYEAFSK
GVVDSIDLPLNISR
HLEINPDHPIVETLR
HSQFIGYPITLYLEK
HSQFIGYPITLYLEKER
KHLEINPDHPIVETLR
KHSQFIGYPITLYLEK
NPDDITQEEYGEFYK
RAPFDLFENK
SIYYITGESK
SIYYITGESKEQVANSADFVER
SLTNDWEDHLAVK
SLVSVTK
TLTLVDTGIGMTK
YESLTDPSKLDGK
YIDQEELNK

aa positions

amino acids 96-107 of SEQ ID NO.: 38
amino acids 558-565 of SEQ ID NO.: 38
amino acids 331-337 of SEQ ID NO.: 38
amino acids 42-53 of SEQ ID NO.: 38
amino acids 42-55 of SEQ ID NO.: 38
amino acids 70-82 of SEQ ID NO.: 38
amino acids 492-502 of SEQ ID NO.: 38
amino acids 429-435 of SEQ ID NO.: 38
amino acids 379-392 of SEQ ID NO.: 38
amino acids 625-639 of SEQ ID NO.: 38
amino acids 205-219 of SEQ ID NO.: 38
amino acids 205-221 of SEQ ID NO.: 38
amino acids 624-639 of SEQ ID NO.: 38
amino acids 204-219 of SEQ ID NO.: 38
amino acids 292-306 of SEQ ID NO.: 38
amino acids 338-347 of SEQ ID NO.: 38
amino acids 482-491 of SEQ ID NO.: 38
amino acids 482-502 of SEQ ID NO.: 38
amino acids 307-319 of SEQ ID NO.: 38
amino acids 532-538 of SEQ ID NO.: 38
amino acids 83-95 of SEQ ID NO.: 38
amino acids 56-69 of SEQ ID NO.: 38
amino acids 276-284 of SEQ ID NO.: 38

Amendments to the Abstract

Please replace the abstract with the following abstract:

The present invention relates to screening methods useful for drug discovery of apoptosis inducing compounds. In particular, the screening methodology relates to using Apoptosis Inducing Proteins (AIPs) as a target for the discovery of apoptosis activators useful as anticancer agents. The screening methods of the present invention can employ homogenous or heterogeneous binding assays using purified or partially purified AIPs; or whole cell assays using cells with altered levels of one or more AIPs. The invention also contemplates use of gambogic acid or GA-related compounds which bind AIPs and can accordingly be used to raise antibodies useful for drug discovery. Alternatively, labeled GA is used for competitive binding assays for drug discovery. Such assays afford high throughput screening of chemical libraries for apoptosis activators.